☐ 1: Oncogene 1995 Sep 21;11(6):1079-88 Related Articles, Books, LinkOut

Vav and Ras induce fibroblast transformation by overlapping signaling pathways which require c-Myc function.

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Recent evidence has suggested that the Vav oncoprotein may function as a hematopoietic-specific GTP exchange factor for the Ras superfamily of proteins. However, transformation of NIH3T3 fibroblast cells by Vav is morphologically distinct from that induced by activated Ras oncogenes, suggesting that the two oncoproteins induce separate signal transduction pathways which promote transformation. To address this issue, the effects of dominant negative mutants of H-ras and proto-Vav (proto-VavR695L, a mutation in the VavSH2 domain) were tested on Vav- and Ras-induced transformation. These mutants partially inhibited both Vav- and Ras-induced transformation, suggesting that they may induce a common downstream signaling pathway which potentiates transformation. As an independent measure of Vav function we also tested the ability of the purified protein encoded by VavSH2 to influence Germinal Vesicle Breakdown (GVBD) during Xenopus oocyte maturation. Microinjection of the VavSH2 protein alone, but not mutant VavR695L SH2 protein, was sufficient to induce GVBD and accelerated maturation induced by normal Ras, suggesting that in this system as well Vav and Ras signals overlap through a common effector. A key target of multiple signalling pathways is c-Myc. Dominant negative versions of c-Myc totally abolished morphologic transformation of NIH3T3 cells by both Vav and Ras oncogenes. These results suggest that distinct, but overlapping, signalling pathways are induced by Vav and Ras and that fibroblast cell transformation by either oncogene requires c-Myc functions.

PMID: 7566967 [PubMed - indexed for MEDLINE]

1: Cancer Gene Ther 1998 Jul-Aug;5(4):236-46

Transgene expression in dendritic cells to induce antigen-specific cytotoxic T cells in healthy donors.

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Immunization with specific tumor-associated antigen (Ag) (TAA)-pulsed dendritic cells (DC) has proven to be efficacious in a variety of animal models and is being investigated for the treatment of cancer patients. Use of DC pulsed with specific peptides or transfected with TAA genes has been a focused area of investigation for the induction of potent tumor and viral immune responses. In this study we demonstrate transgene expression, including expression of the MART-1 gene, in DC transfected with plasmid DNA and cationic liposome complexes. These transiently transfected DC, derived from healthy donor monocytes cultured with granulocyte macrophage colony-stimulating factor and interleukin-4, express the transgene and can stimulate naive CD8+ T cells to elicit an antitumor immune response. These cytotoxic T lymphocytes (CTL) were capable of recognizing both known and unknown TAA epitopes and were able to exhibit cytolytic activity against human histocompatibility leukocyte Ag-matched tumor cells expressing the Ag. In addition to their cytolytic function, the CTL displayed an oligoclonal T-cell receptor repertoire, indicating that the presented Ag induced alterations in the T-cell population. The ability to induce tumor-specific CTL in vitro using gene-modified DC transiently expressing TAAs demonstrates the potential use of these Ag-presenting cells to generate future in vivo cancer vaccine strategies.

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1: Oncogene 1991 Jul;6(7):1259-68

The stimulation of quiescent rat fibroblasts by v-src and v-fps oncogenic protein-tyrosine kinases leads to the induction of a subset of immediate early genes.

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The stimulation of quiescent murine fibroblasts by growth factors and by phorbol esters results in a rapid and transient transcriptional activation of a large group of so-called immediate early genes. Several such genes were found to be induced in chicken embryo fibroblasts following activation of a temperature sensitive (ts) Rous sarcoma virus $v_7$src mutant following temperature shift (Simmons et al., 1989). In contrast, the classical immediate early genes c-myc, c-fos and c-jun were essentially uninducible upon activation of a ts v-src mutant in rat-1 fibroblasts (Welham et al., 1990). We have cloned 9 cDNAs of genes that are rapidly and transiently inducible in rat fibroblasts by ts v-src mutants, and by a ts Fujinami sarcoma virus v-fps mutant. Six of these cDNAs are derived from the known immediate early genes NGFI-A, KC, c-fos, tissue factor, PC4 and ornithine decarboxylase; the other three cDNAs have not been described before. These 9 genes showed individual profiles of inducibility by fetal calf serum, epidermal growth factor (EGF) and by phorbol esters. Their response to the retroviral oncogenic protein-tyrosine kinases correlated best with the one to EGF, suggesting a common pathway of signal transduction. c-fos did not respond strongly to this pathway but was well induced by fetal calf serum. NGFI-A, however, was induced to a similar extent by all activators tested. Furthermore, we demonstrated that the induction of several of these genes by the retroviral oncogenic protein-tyrosine kinases is rapid, direct and occurs at the transcriptional level.

PMID: 1861868 [PubMed - indexed for MEDLINE]

1: Biokhimiia 1994 Nov;59(11):1766-73 Related Articles, Books

[Regulation of the cycle of phospholipid turnover in hamster fibroblasts transformed by v-src and N-ras oncogenes]

[Article in Russian]

Krasil'nikov MA, Shatskaia VA, Shtutman MS.

The phospholipid turnover has been studied in two lines of golden hamster cells: in cells transformed by the Rous sarcoma virus (line HET-SR) and in cells additionally transfected with the activated oncogene N-ras (line HET-SR-N-ras, clone 6). It has been found that HET-SR cells are distinguished by a high level of phosphatidylcholine turnover and a relatively low level of phosphoinositide turnover. Transfection of cells with the activated N-ras (line HET-SR-N-ras) leads to the inhibition of phosphatidylcholine synthesis and activation of phosphoinositide metabolism. Both cell lines preserve their sensitivity to serum growth factors stimulating the rate of phospholipid turnover. In both cell lines dexamethasone decreases the rate of DNA synthesis and inhibits the phosphatidylcholine and phosphoinositide turnover. At the same time, dexamethasone does not influence the predominant activation of phosphatidylcholine synthesis in HET-SR cells or the activation of phosphoinositide synthesis characteristic of HET-SR-N-ras cells. The data obtained suggest that the transmission of the mitogenic signal from growth factor in HET-SR and HET-SR-N-ras cells occurs via the activation of the phospholipid turnover and is controlled by steroid hormones. The role of v-src and N-ras oncogens in the transmission of the mitogenic signal seems to be insignificant; their activity is not controlled by dexamethasone.

PMID: 7873683 [PubMed - indexed for MEDLINE]

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